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(71) Applicant *(for all designated States except US)*: IDI FARMACEUTICI S.P.A. [IT/IT]; Via dei Castelli Romani, 83/85, I-00040 Pomezia (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PASSI, Siro [IT/IT]; Via Etna, 7, I-00141 Roma (IT). GUARNIERI, Decimo [IT/IT]; Via dei Castelli Romani, 83/85, I-00040 Pomezia (IT). CARBONE, Santo [IT/IT]; Via Stradella, 169, I-04100 Latina (IT).

(74) Agents: BORRINI, Stefano et al.; Società Italiana Brevetti S.p.A., Piazza di Pietra, 39, I-00186 Roma (IT).

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(57) **Abstract**

The present invention relates to a dietary product comprising ubiquinone, stabilised vitamin E, phospholipids, selenium in an organic form and L-methionin, which is effective to combat cell oxidative stress even to the extreme consequences thereof, for example cell decay, acquired and/or congenital immunodeficiency or other alterations in the immune system. The dietary product object of the present invention is also effective as a coadjutant in the treatment of apoptosis, in mutagenesis and/or carcinogenesis, in infectious diseases of viral or bacterial origin or those deriving from other external pathogens, in myelinic and skin diseases, in cardiovascular diseases and in allergies.

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COMPOSITION OF A DIETARY PRODUCT THAT IS EFFECTIVE TO COMBAT OXIDATIVE STRESS AND CELL DECAY

DESCRIPTION

The cell antioxidant pool is essentially made up of enzymatic antioxidants (Cu-Zn, superoxide dismutase - SOD, glutathione peroxidase-GSH-Px, catalase-CAT), of non-enzymatic lipophilic (RRR-α-tocopherol-vitamin E and ubiquinol-$CoQ_{10}H_2$-) and hydrophilic (glutathion-GSH, urates, albumin) antioxidants and of proteic transition metal ion sequestrating agents (ferritin, transferrin, ceruloplasmin) (see bibliographic references 1-7).

Each molecule has a specific biological function: for example the vitamin E and the ubiquinol are concentrated in the cell and sub-cell membranes with the main role of inhibiting lipo-peroxidation induced by oxygen reactive species (ROS) and other radicals on the unsaturated structures of the membranes, in particular the polyunsaturated fatty acids (PUFA); SOD, GSG-Px and CAT are responsible for removal of O_2 and H_2O_2, respectively.

Human cells have an antioxidant pool sufficient to counteract the normal physiological production of oxygen reactive species (ROS) and other free radicals; however the naturally present antioxidant pool is not capable of counteracting an increase in generation of ROS; in these cases, so-called "oxidative stress" occurs (see bibliographic reference 2).

From the above it can be seen that the insurgence of "oxidative stress" can be caused by two phenomena: the first is the lack of antioxidant molecules, and the second is the uncontrolled increase of oxygen reactive species (ROS) and free radicals, which are able to cause irreversible oxidation not only of the polyunsaturated fatty acids (PUFA), but also of proteins, nucleic acids and sugars. Oxidative stress is present to a varied extent in a number of serious diseases in man: while this does not mean that oxidative stress is the cause of these

diseases, it does testify, as confirmed by a number of studies, that oxidative stress can have a negative influence on the progress of said diseases, causing further damage to the cells of an organism that is already sick (see bibliography and references 1 and 2).

It has now surprisingly been found that a dietary product comprising ubiquinone (CoQ_{10}), stabilised vitamin E, phospholipids, selenium of organic origin and L-methionin, by acting both on the cell wall reconstitution mechanisms, and consequently on that of the phospholipids forming it, and on the reintegration of glutathione and glutathione peroxidase, helps to combat cellular oxidative stress in an effective manner.

Oxidative stress appears significantly involved in certain diseases with a serious social impact, such as AIDS, seborrheic dermatitis, atopic dermatitis, leprosy, multiple sclerosis, in which genetic factors, malnutrition and/or under-nourishment, an incongruous lifestyle, the use of drugs and toxic substances, have an important etiologic role. It has been found that in the blood of patients suffering from these diseases, the significant deficiency of ubiquinole-ubiquinone, vitamin E, glutathione and glutathione peroxidase (GSH and GSH-Px), which is more or less marked according to contingent conditions, is associated with a deficiency of polyunsaturated fatty acids (PUFA) in the phospholipids (see references 8-12). According to the state of the art, administration of the molecules identified above to patients suffering from seborrheic and atopic dermatitis is simply and generally described, although said administration takes place in a separate and non-homogeneous manner, and this type of administration has actually shown extremely promising results (see references 11-12).

An object of the present invention is therefore a composition comprising:

Ubiquinone 5-8%

Stabilised vitamin E	12-15%
Polyunsaturated phospholipids	45-52%
Organic selenium	2-5% (corresponding to 0.1-3% ionic selenium)
L-methionin	23-32%

along with the usual tolerated vehicles

A further object of the present invention is a composition for a dietary product comprising:

Ubiquinone	5-8%
Stabilised vitamin E	12-15%
Polyunsaturated phospholipids	45-52%
Organic selenium	2-5% (corresponding to 0.1-3% ionic selenium)
L-methionin	23-32%

along with the usual pharmaceutically tolerated vehicles.

The percentages indicated are expressed as a percentage by weight with reference only to the total weight of the active ingredients in the composition of the dietary product.

A further object of the present invention is the use of the composition for preparation of a dietary product that is effective in combating oxidative stress and cell decay.

A further object of the present invention is the use of the composition indicated above to produce a dietary product effective as a coadjutant in the treatment of mechanisms of mutagenesis and carcinogenesis, of immuno-deficiency mechanisms, or other alterations of the immune system, of diseases of myelinic origin or other pathologies deriving from a progressive alteration in the neurotransmission mechanisms, of skin diseases and of cardio-vascular diseases.

A further object of the present invention is the use of the composition mentioned above to prepare a dietary product coadjutant in the treatment of infectious

diseases of viral or bacterial origin, and those deriving from other external pathogens, of tuberculosis, of leprosy, of herpes simplex labialis or genetalis, of AIDS, of multiple sclerosis, of atopic dermatitis, of vitiligo, in vaccination against allergies or other alterations of the immune system, of diseases of myelinic origin or other pathologies deriving from a progressive alteration in the neurotransmission mechanisms.

The present description comprises fifteen figures which show, in graph form, the influence of administration of a composition according to the present invention to the patients who will be more clearly specified in example 3 in case of figures 1 to 9 and in example 4 in case of figures 10 to 15:

figure 1 shows the vitamin E concentration in the blood plasma versus time;

figure 2 shows the blood plasma concentration of oxidised and reduced ubiquinone (total ubiquinone) versus time;

figure 3 shows the concentration of vitamin E (expressed as micrograms of vitamin E in the lymphocytes per ml of blood) in the lymphocytes versus time;

figure 4 shows the reduced glutathione concentration in the erythrocytes versus time;

figure 5 shows the glutathione peroxidase concentration in the erythrocytes versus time;

figure 6 shows the trend of the palmitic acid concentration in the plasma versus time;

figure 7 shows the trend of the diomo-γ-linolenic acid concentration in the plasma versus time;

figure 8 shows the trend of the arachidonic acid concentration in the plasma versus time;

figure 9 shows the trend of the docosahexanoic acid concentration in the plasma versus time;

figure 10 shows the vitamin E concentration in the blood plasma versus time in a different population of patients as those referred to in figures 1 to 9;

figure 11 shows the blood plasma concentration of total ubiquinone versus time;

figure 12 shows the concentration of vitamin E in the lymphocytes versus time;

figure 13 shows the reduced glutathione concentration in the erythrocytes versus time;

figure 14 shows the glutathione peroxidase concentration in the erythrocytes versus time; and

figure 15 shows the arachidonic acid concentration in plasma.

In the following examples concerning the production, composition and formulation of compositions for dietary products according to the present invention as well as the evaluation of the effect of its administration are reported.

Example 1

The present example relates to the production of a pill with the following qualitative and quantitative composition:

Ubiquinone	mg 12.50	(6.74% by weight)
RRR-α-tocopheryl acetate 50%	mg 26.65	(14.37% by weight)
Soy lecithin	mg 90.00	(48.54% by weight)
Selenium aspartate	mg 6.25	(3.37% by weight)
L-methionin	mg 50.00	(26.97% by weight)
Other excipients to make	g 1.50	

The percentages expressed refer to the total weight of the active components of the composition, without taking into account the excipients. Particularly preferred excipients are those that can be used to formulate a compound that can be chewed; among said excipients it is possible to mention mannitol, cellulose, flavouring, magnesium stearate, silica. The vitamin E acetate is of the type obtained by direct compression, and it is therefore additioned with 50% of inert substances suitable to help compression.

The amount of selenium aspartate indicated corresponds to 12.5 µg of selenium in ionic form.

Excipients are added to the above mixture of components, which are then subjected to a further mixing stage, and following this to compression in the laboratory. Pills of 1.5 g each are obtained, with a thickness of 6 mm.

Example 2

Preparation of an industrial batch of pills having the same qualitative and quantitative composition described in example 1.

Ubiquinone	kg 1.250
RRR-α-tocopheryl acetate 50%	kg 2.665
Soy lecithin	kg 9.000
Selenium aspartate	kg 0.625
L-methionin	kg 5.000
Other excipients to make	kg 150

To the mixture of components listed above are added the excipients (mannitol, cellulose, flavouring, magnesium stearate, silica). A further mixing stage is then performed, after which the pills are formed using an industrial press of a per se known type. Pills weighing 1.5 g each and with a thickness of 6 mm are obtained.

The polyunsaturated fatty acids and the vitamin E employed in the compositions according to the present invention have been analysed by means of capillary gas chromatography-mass spectrometry (see reference 8). The ubiquinole/ubiquinone and GSH/GS-SG redox pairs by HPLC (see references 13-14); the superoxide dismutase, glutathione peroxidase and catalase activities (respectively SOD, GSH-Px and CAT) by spectrophotometry (see references 15-17) using the procedures indicated in each of the relative references. The vitamin E used in the composition of the dietary product according to the present invention was analysed both in the composition and in the blood plasma after administration, by means of HPLC on chiral phase (see bibliographic reference No. 18).

Example 3

This example gives an evaluation of the effects of administration of four pills per day, with the following qualitative and quantitative composition, to a certain number of volunteers who will be further described in the following.

The composition was as follows:

Ubiquinone	mg 12.50
RRR-α-tocopheryl acetate 50%	mg 26.65
Soy lecithin	mg 90.00
Selenium aspartate	mg 6.25
L-methionin	mg 50.00
Other excipients to make	g 1.50

The pills were administered daily during meals, for one month to 60 volunteers, half male and half female, aged between 25 and 42 years. The volunteers represented the following: 20 healthy individuals (controls), 20 seropositive HIV patients (HIV+) suffering from seborrheic dermatitis (DS), 20 seronegative HIV patients (HIV-) also suffering from seborrheic dermatitis.

A diet rich in polyunsaturated fatty acids was recommended for the patients suffering from seborrheic dermatitis. At the start of treatment, after 15 days and 30 days after the end of treatment the following parameters were measured for each individual:

a) The blood levels of phospholipids-polyunsaturated fatty acids, vitamin E, oxidised and reduced ubiquinone (total ubiquinone);

b) The levels of vitamin E in the lymphocytes;

c) Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activity in the erythrocytes;

d) The levels of reduced and oxidised glutathione (GSH and GS-SG) in the erythrocytes. The results are shown in the following tables 1 and 2, and exemplified in figures 1, 2, 3, 4, 5, 6, 7, 8 and 9.

From the results it can be observed that:

- vitamin E (in the plasma and in the lymphocytes) increases both in HIV+ and in HIV- patients, and in the controls (see table 1 and figures 1 and 3).

- total ubiquinone (oxidised and reduced) increases significantly in HIV+ patients. Less significant increases can also be seen in HIV- patients and in the controls (see table 1 and figure 2).

- The reduced glutathione increases significantly in HIV+ patients. Less significant increases are also found in HIV- patients and in the controls (see table 1 and figure 4).

- The glutathione peroxidase increases in HIV+ and HIV- patients. It remains stable in the controls (see table 1 and figure 5).

- The palmitic acid decreases significantly in HIV+ and HIV- patients. It remains stable in the controls (see table 2 and figure 6).

- The diomo-gamma-linolenic, arachidonic and docohexaenoic acids increase significantly in HIV+ and HIV- patients. They remain stable in the controls (see table 2 and figures 7, 8 and 9).

Example 4

In the present example the effect of the administration of a variable daily quantity of pills (according to individual needs) of the following quali-quantitative composition at a certain number of patients better specified in the following.

The composition is the following:

Ubiquinone	mg 12.50
RRR-α-tocopheryl acetate 50%	mg 26.65
Soy lecithin	mg 90.00
Selenium aspartate	mg 6.25
L-methionin	mg 50.00
Other excipients to make	g 1.50

The pills have been administered daily during the meals for one month to fifty voluteers males aged between 33 and 55 years. The volunteers were civil aviation

pilots in service. The pilots have been chosen in order to evaluate the effect of the composition according to the present invention on patients whose work and lifestyle is known to provoke stress. For each individual at the beginning and after ninety days of treatment, the following parameters have been evaluated; as a control the values obtained on the control group analyzed at zero time and made up of healthy individuals have been chosen:

a) The plasma levels of phospholipids-polyunsaturated fatty acids, of vitamin E, of oxidised and reduced ubiquinone (total ubiquinone);

b) The lymphocyte levels of vitamin E;

c) The acitivy in the erythrocytes of glutathione peroxidase (GSH-PX);

d) The levels in the erythrocytes of reduced and oxidised glutathione (GSH and GS-SG).

From the obtained results exemplified in figures 10, 11, 12, 13, 14 and 15, it may be observed, at least at qualitative level, that:

vitamin E (in blood plasma and lymphocytes) increases in comparison with the control group (see figures 10 and 12);

the total ubiquinone (oxidised and reduced) significantly increases in comparison with the control group (see figure 11);

the reduced glutathione significantly increases in comparison with the control group (see figure 13);

the glutathione peroxidase increases in comparison with the control group (see figure 14); and

the arachidonic acid significantly increases in comparison with the control group (see figure 15).

Table 1

Hematic levels of antioxidants in controls and in HIV+ and HIV- patients suffering from seborrheic dermatitis before, during and after treatment with the composition according to the present invention.

The results are expressed as an average ± SD

* P<0.001 vs controls at t=0

° p<0.01 vs controls at t=0

	CONTROLS (No=20)			HIV+ (No=20)			HIV- (No=20)		
Antioxidants	t=0d	t=15 d	t=30 d	t=0d	t=15 d	t=30 d	t=0d	t=15 d	t=30
					PLASMA				
Vit. E (µg/ml)	11.3±1.9	15.6±2.8*	19.4±4.1*	7.9±2.6*	11.9±2.7	15.5±5.3*	9.3±1.4*	14.7±2.2°	16.5±3
CoQ10H2 (µg/ml)	0.48±0.11	0.66±0.09*	0.75±0.15*	0.08±0.10*	0.15±0.09*	0.21±0.11*	0.35±0.09*	0.45±0.12	0.56±0
CoQ10 (µg/ml)	0.43±0.10	0.47±0.08	0.55±0.08*	0.32±0.10°	0.4±0.13	0.74±0.14*	0.48±0.11	0.60±0.15	0.50±0
								°	
					LYMPHOCYTES				
Vit. E (µg/ml blood)	75±21	88±27	105±35*	48±19+	53±19°	59±22	60±15°	70±23	86±28
					ERYTHROCYTES				
GSH (µg/ml blood)	270±98	285±90	297±88	185±66*	212±18°	230±70	240±89	266±61	283±74
GS-SG (µg/ml blood)	23±14	26±12	30±11	34±15	30±14	32±23	26±12	28±10	27±14
SOD (U/g Hb)	676±141	66'±150	645±178	919±290*	905±180*	891±167*	710±127	688±141	692±14
CAT (U/mg Hb)	280±33	275±40	285±38	298±31	303±42	314±46	275±41	293±26	291±33
GSH-Px (U/g Hb)	708±185	680±166	720±187	303±200*	346±188*	385±196*	498±126*	503±163*	608±14

Table II

Fatty acids (%) of plasma phospholipids in controls and in HIV+ and HIV- patients suffering from seborrheic dermatitis, before, during and after treatment with the composition according to the present invention. Each result is expressed as an average ± SD

* P<0.001 vs controls at t=0

° p<0.01 vs controls

	CONTROLS (No=20)			HIV+ (No=20)			HIV- (No=20)		
Fatty acids	t=0d	t=15 d	t=30 d	t=0d	t=15 d	t=30 d	t=0d	t=15 d	t=30 d
C16:0	26.8±1.4	26.0±2.1	26.2±2.3	30.0±2.1°	29.6±2.6°	27.7±2.6	28.5±2.4	28.2±3.0	26.4±2.5
C18:0	15.9±1.7	14.2±1.9	15.0±1.8	18.8±2.7°	18.6±4.0°	16.4±3.1	18.0±2.6	17.0±2.4	15.8±2.7
C18:1	13.1±2.2	14.3±2.0	13.9±1.7	15.8±2.6°	14.8±3.1	14.3±2.5	15.0±3.3	14.6±2.8	114.3±2.0
C18:2 n-6	25.3±2.3	24.8±3.1	24.6±3.4	23.9±5.2	23.5±2.5	24.0±3.2	24.1±6.1	24.0±3.2	24.5±3.0
C20:3 n-6	3.9±0.6	3.8±1.0	3.7±0.8	1.9±0.1*	2.0±0.5*	2.9±0.7°	2.3±0.5*	2.6±0.7*	3.3±1.1
C20:4 n-6	12.7±1.8	12.4±1.5	12.2±1.8	7.7±2.8	8.4±2.5*	10.9±1.5°	9.5±2.4*	10.3±1.6*	12.3±1.7
C22:6 n-3	3.8±0.9	3.5±0.7	3.4±0.7	1.4±0.1*	1.8±0.4*	2.6±0.5*	1.8±0.6*	2.2±0.8*	3.1±0.9
others	1.2	1.0	1.0	0.5	1.3	1.2	0.8	0.9	0.5

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CLAIMS

1. A composition characterised by the fact of comprising:

Ubiquinone	5-8%
Stabilised vitamin E	12-15%
Polyunsaturated phospholipids	45-52%
Organic selenium	2-5% (corresponding to 0.1-3% ionic selenium)
L-methionin	23-32%

along with usual tolerated vehicles, the percentages by weight being expressed as a percentage by weight with reference to the total weight of the active ingredients in the composition.

2. A composition for a dietary product characterised by the fact of comprising:

Ubiquinone	5-8%
Stabilised vitamin E	12-15%
Polyunsaturated phospholipids	45-52%
Organic selenium	2-5% (corresponding to 0.1 3% ionic selenium)
L-methionin	23-32%

along with usual pharmaceutically tolerated vehicles, the percentages by weight being expressed as a percentage by weight with reference to the total weight of the active ingredients in the composition.

3. A composition according to claim 1 or 2, characterised in that it contains said polyunsaturated phospholipids in the form of soy lecithin, said organic selenium in the form of selenium aspartate and said stabilised vitamin E in the form of 50% RRR-α-tocopherol acetate.

4. A composition according to any of the preceding claims, characterised in that it contains the single components in the following percentages:

Ubiquinone	6.74 %

RRR-α-tocopheryl acetate 50%	14.37 %
Soy lecithin	48:54 %
Selenium aspartate	3.37 %
L-methionin	26.97 %

along with the usual tolerable vehicles, the percentages being expressed as percentages by weight with reference to the total weight of the active components in the composition.

5. A composition as claimed in any of the preceding claims, characterised in that it is formulated as a chewable pill.

6. Use of the composition as claimed in any of the claims 1 to 5 for the preparation of a dietary product that is effective in combating oxidative stress and cell decay.

7. Use of the composition as claimed in any of the claims 1 to 5 for preparation of a dietary product that is effective in the treatment of apoptosis, mutagenesis and carcinogenesis mechanisms, of acquired or congenital immuno-deficiency mechanisms or other alterations of the immune system, of diseases of myelinic origin or other pathologies deriving from a progressive alteration in the neurotransmission mechanisms, of skin diseases and of cardio-vascular diseases.

8. Use of the composition as claimed in any of the claims 1 to 5 for preparation of a dietary product that is of assistance in the treatment of infectious diseases of viral or bacterial origin, and those deriving from other external pathogens, in the treatment of tuberculosis, in the treatment of leprosy, in the treatment of herpes simplex labialis or genetalis, in the treatment of AIDS, in the treatment of multiple sclerosis, in the treatment of atopic dermatitis and vitiligo, and in vaccination against allergies.

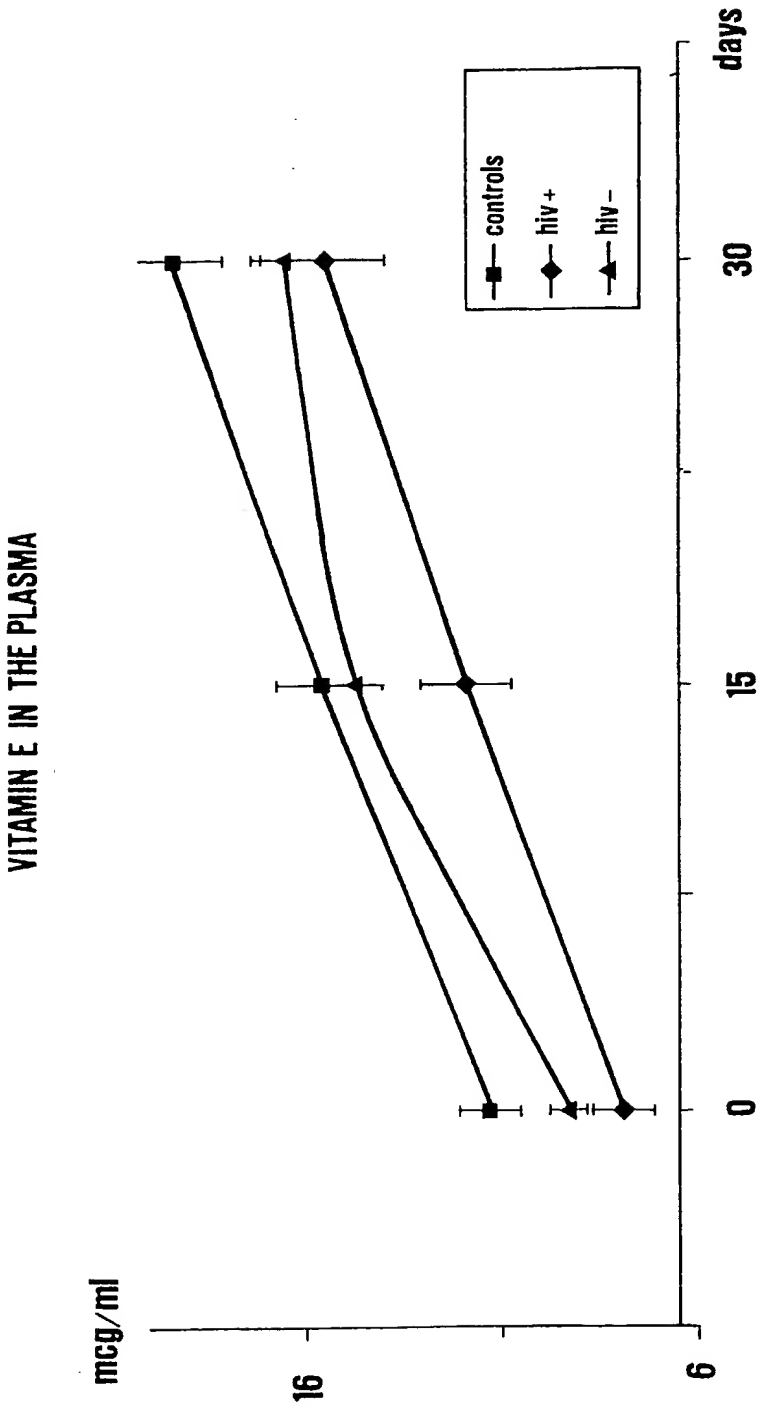
VITAMIN E IN THE PLASMA
mcg/ml
16
6
0
15
30
days
controls
hiv+
hiv-

FIG.1

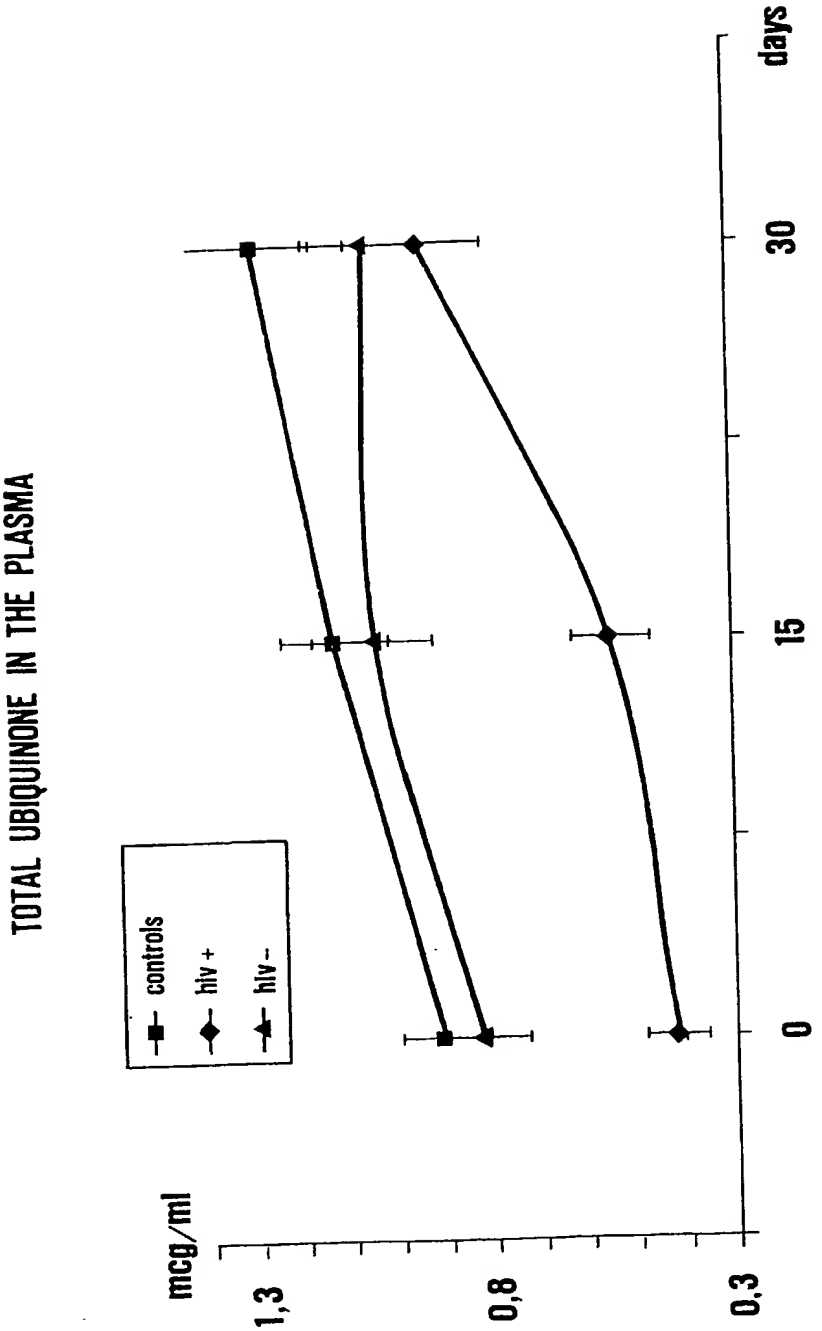
TOTAL UBIQUINONE IN THE PLASMA
controls
hiv +
hiv -
mcg/ml
1,3
0,8
0,3
0
15
30
days

FIG.2

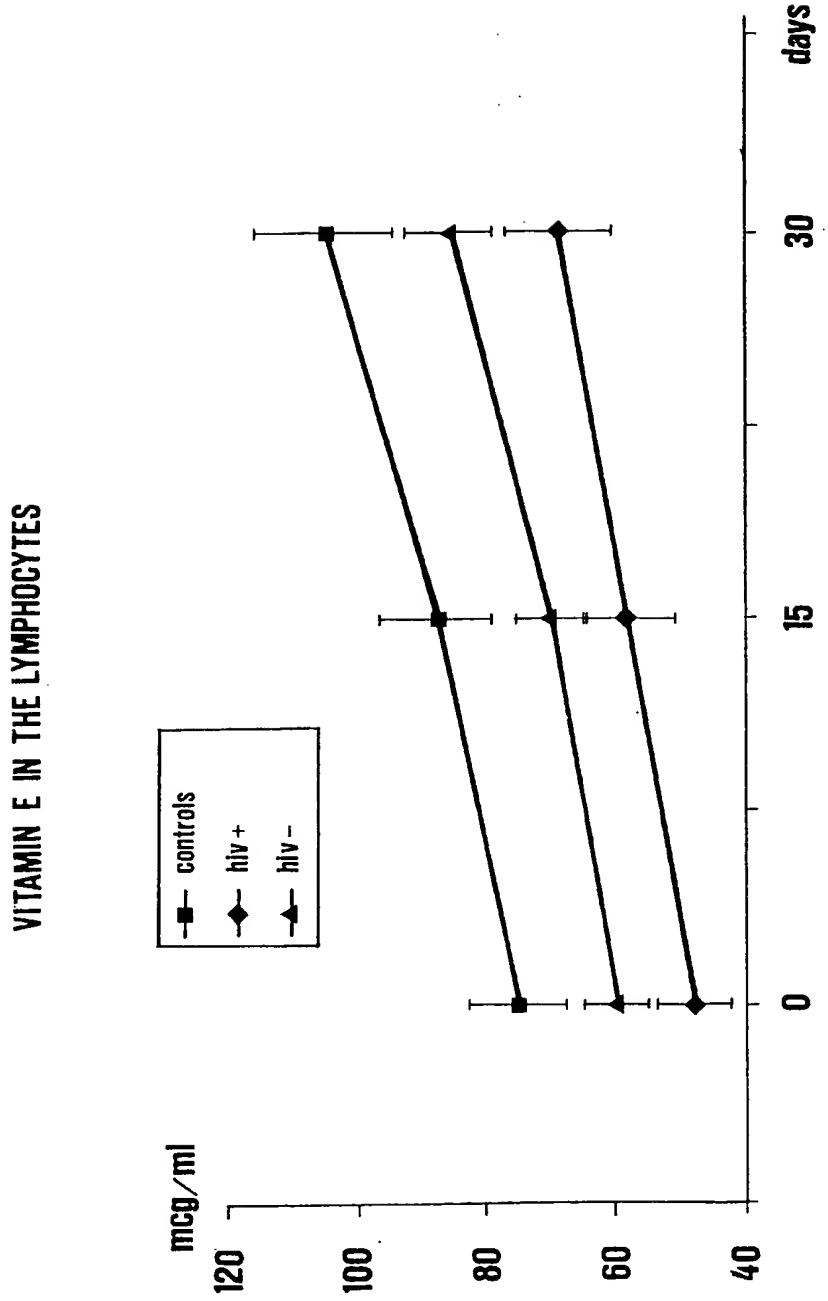
VITAMIN E IN THE LYMPHOCYTES
controls
hiv +
hiv -
mcg/ml
120
100
80
60
40
0
15
30
days

FIG.3

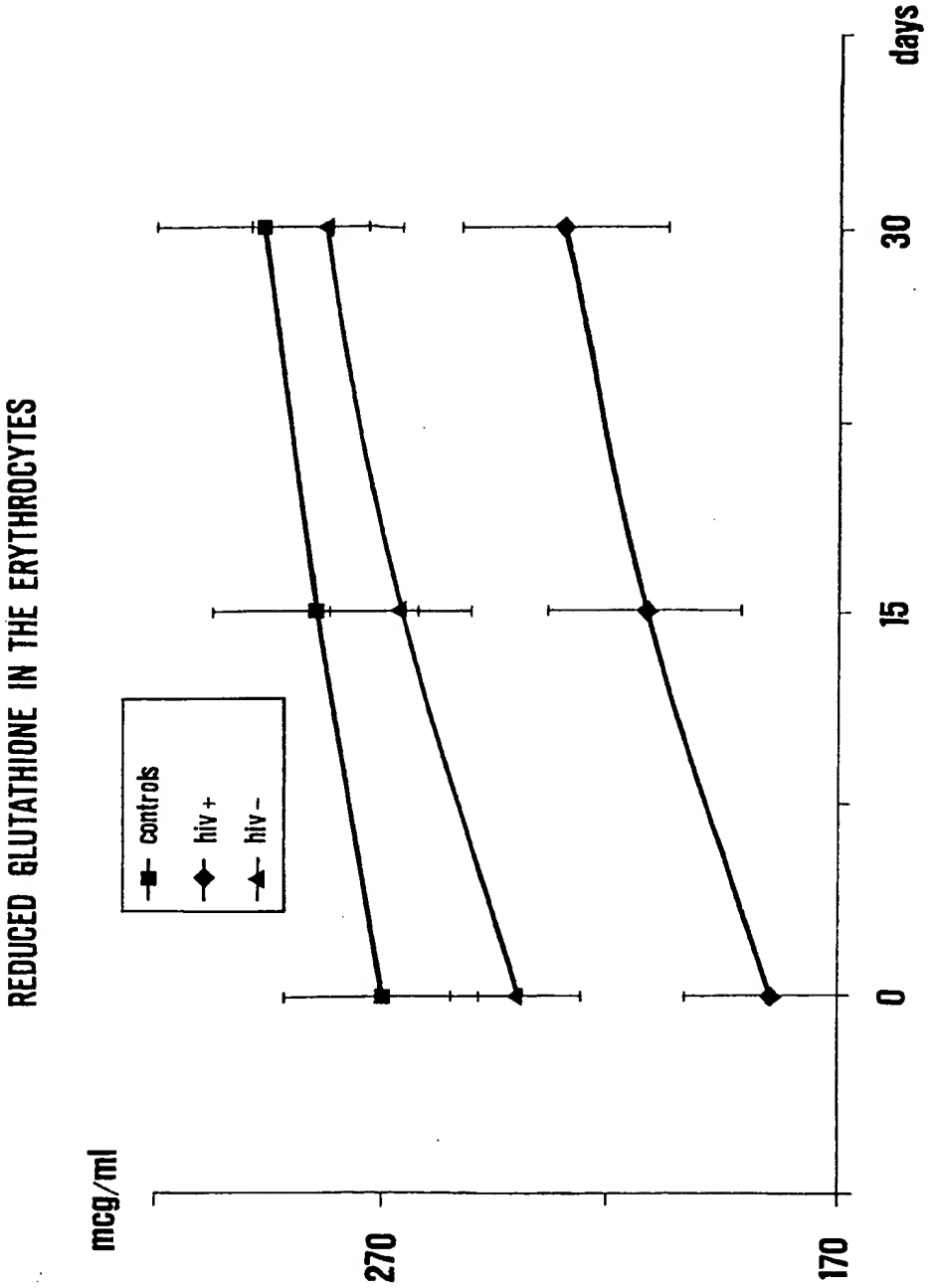
REDUCED GLUTATHIONE IN THE ERYTHROCYTES
mcg/ml
270
170
0
15
30
days
controls
hiv +
hiv -

FIG.4

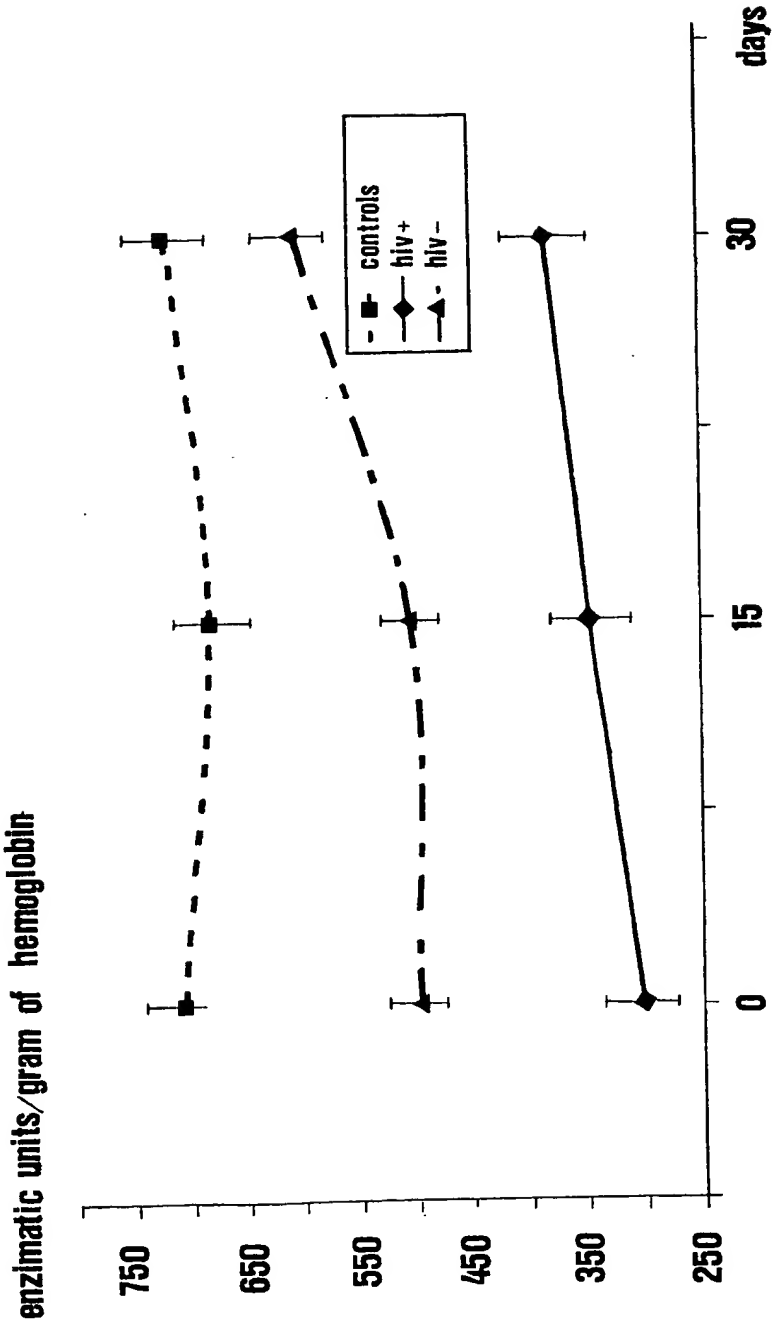
GLUTATHIONEPEROXIDASE IN THE ERYTHROCYTES
enzimatic units/gram of hemoglobin
750
650
550
450
350
250
0
15
30
days
controls
hiv+
hiv-

FIG.5

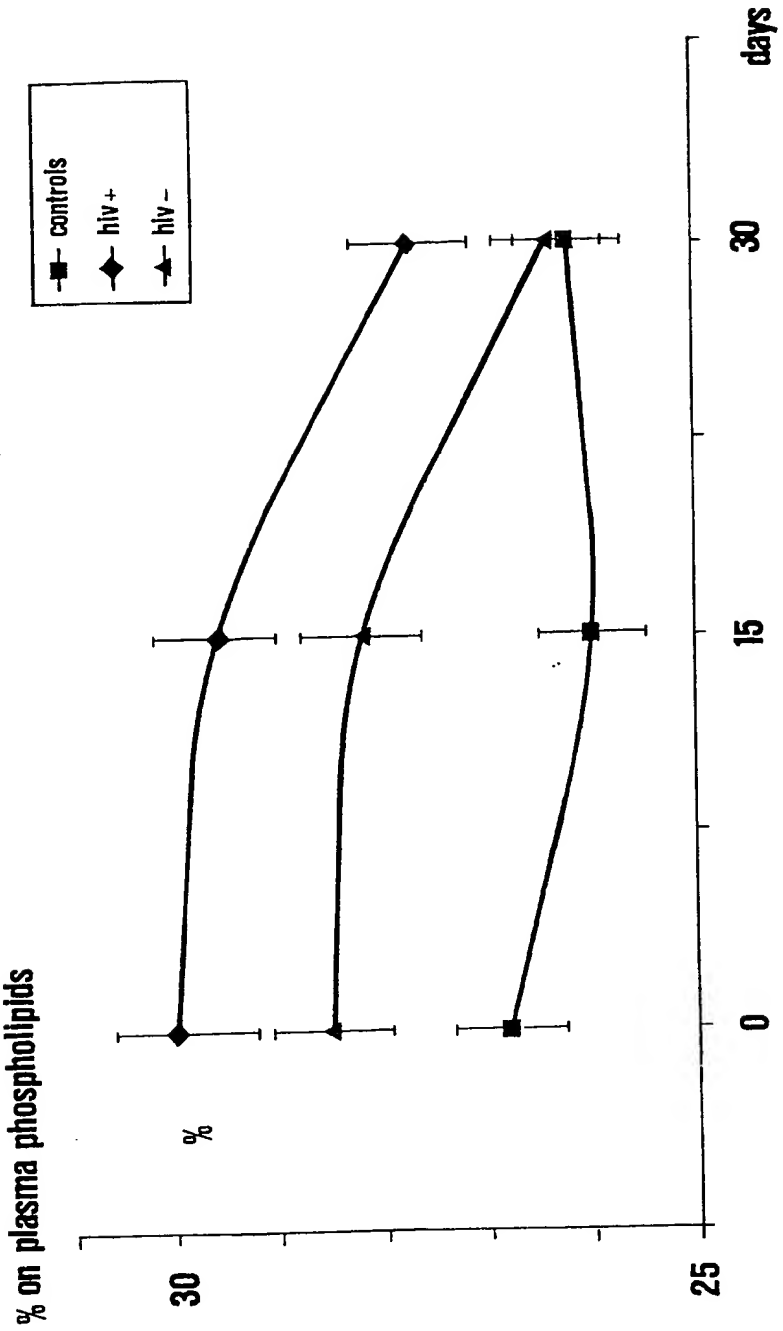
PALMITIC ACID IN THE PLASMA
% on plasma phospholipids
%
30
25
0
15
30
days
controls
hlv +
hlv –

FIG.6

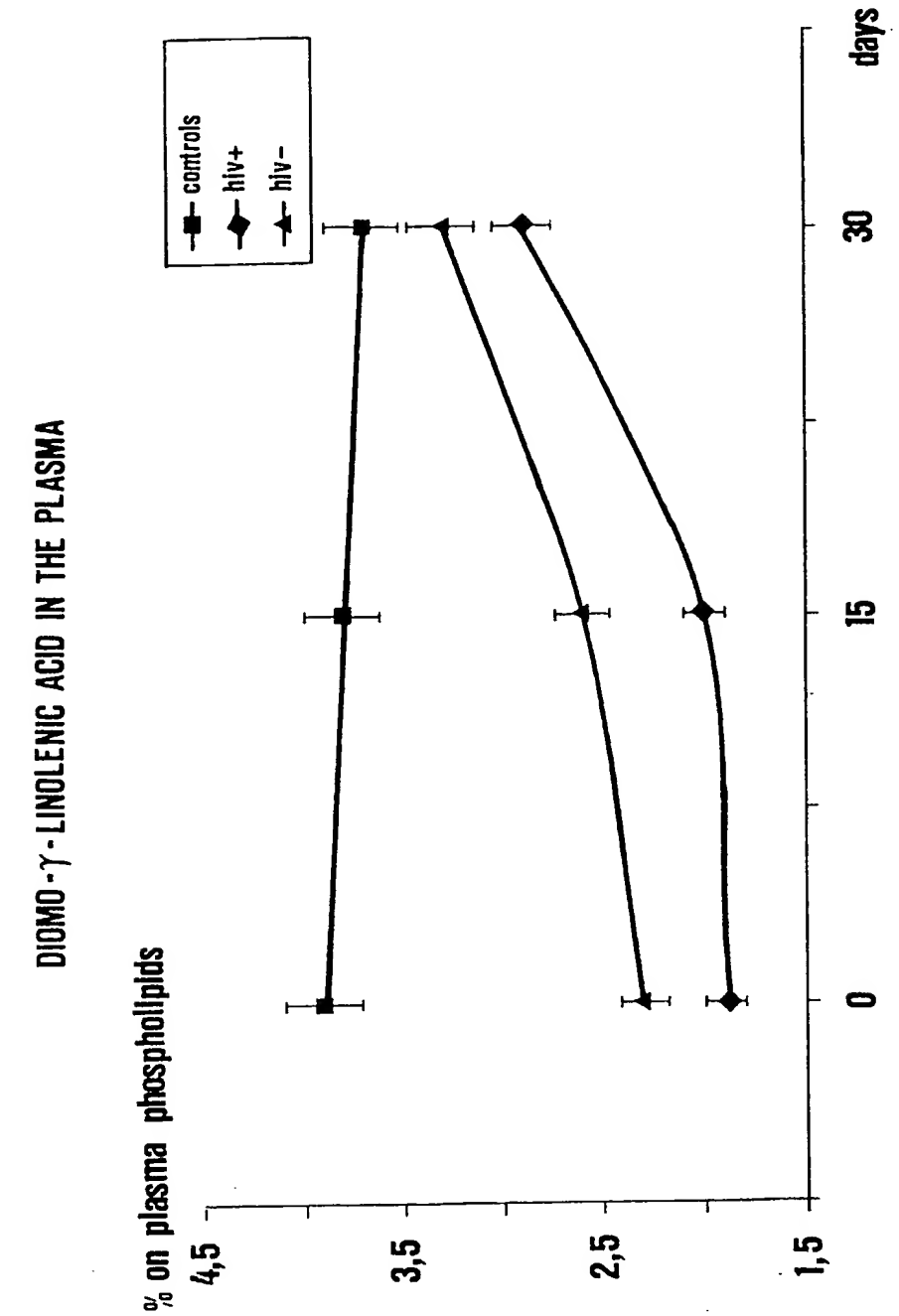
DIOMO-γ-LINOLENIC ACID IN THE PLASMA
% on plasma phospholipids
4,5
3,5
2,5
1,5
0
15
30
days
controls
hiv+
hiv-

FIG.7

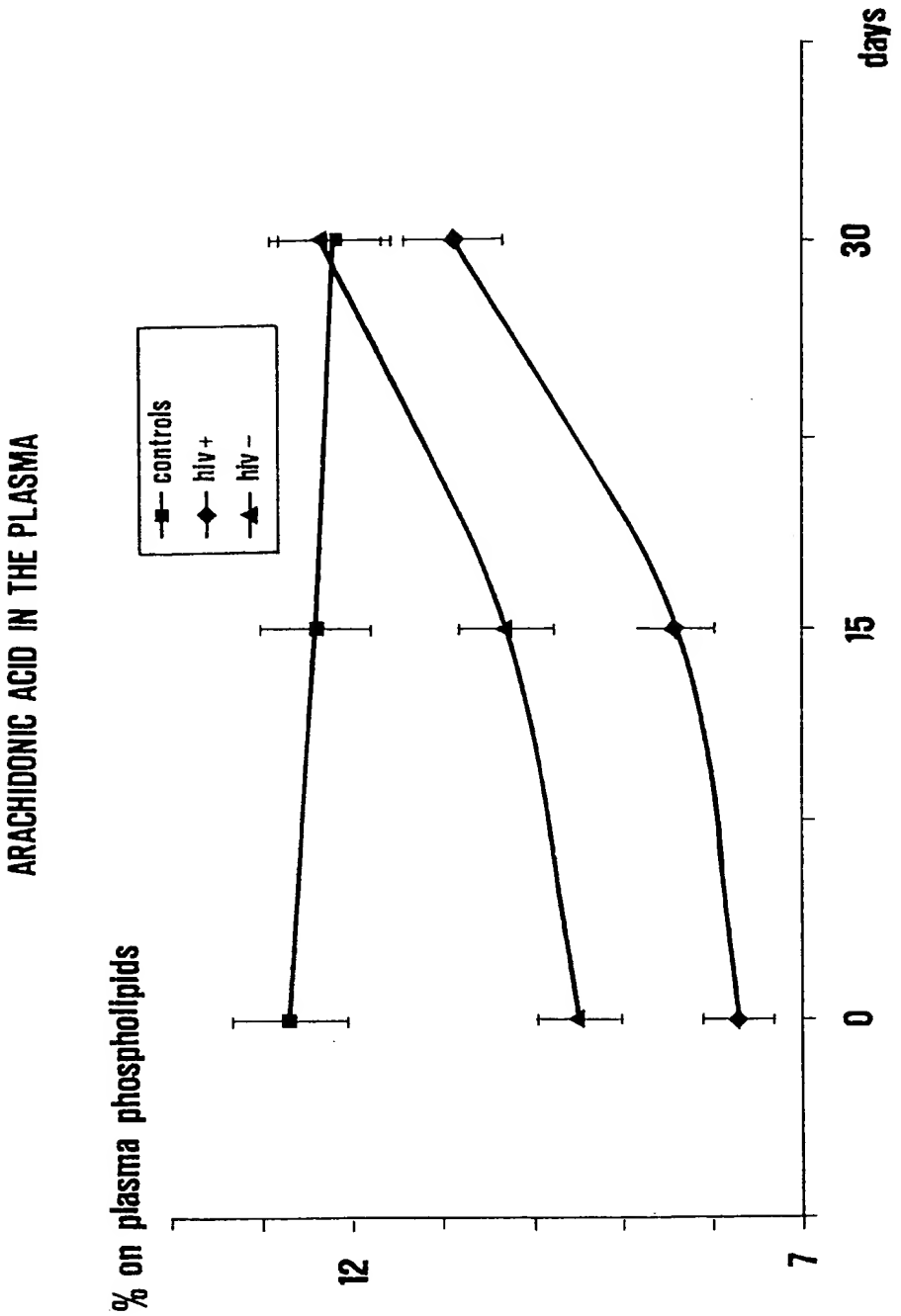
ARACHIDONIC ACID IN THE PLASMA
% on plasma phospholipids
12
7
0
15
30
days
controls
hiv +
hiv -

FIG.8

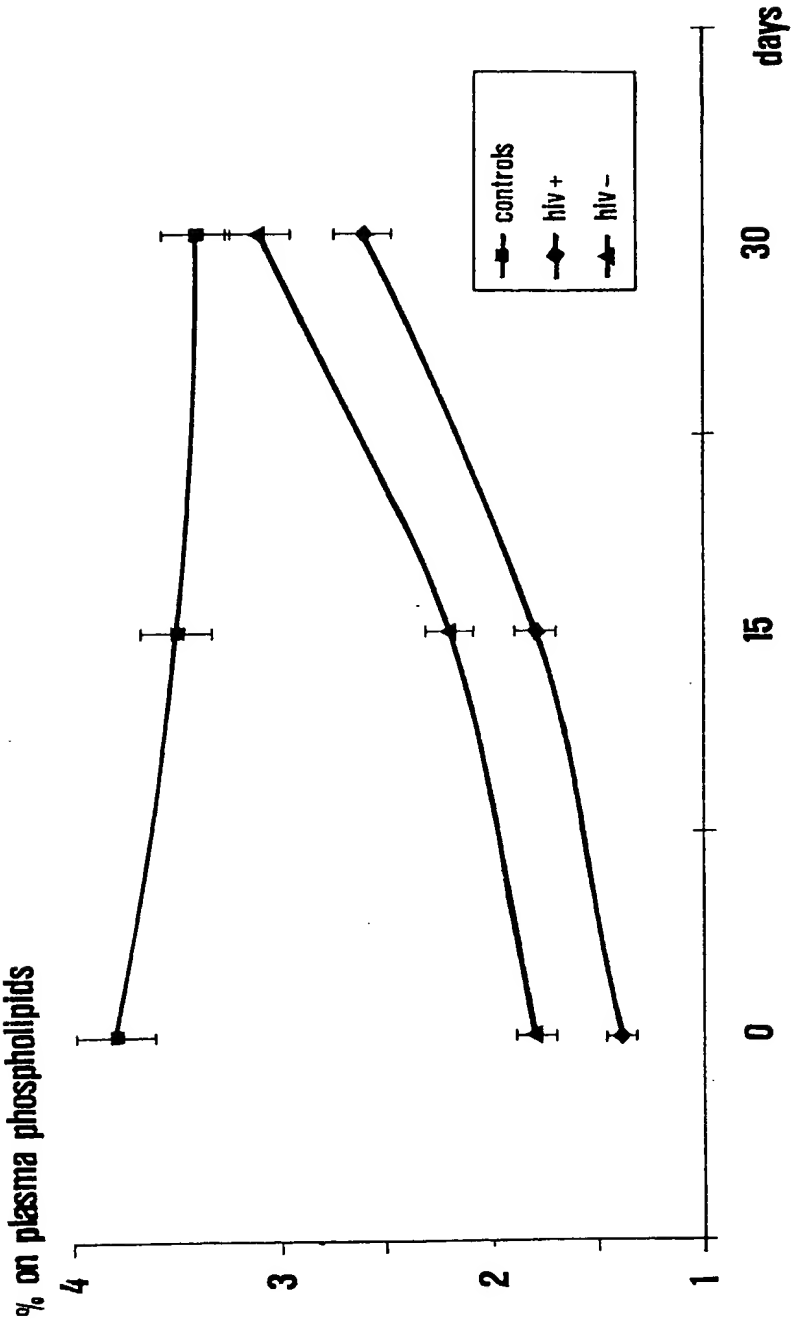
DOCOSAHEXANOIC ACID IN THE PLASMA
% on plasma phospholipids
4
3
2
1
0
15
30
days
controls
hiv +
hiv -

FIG.9

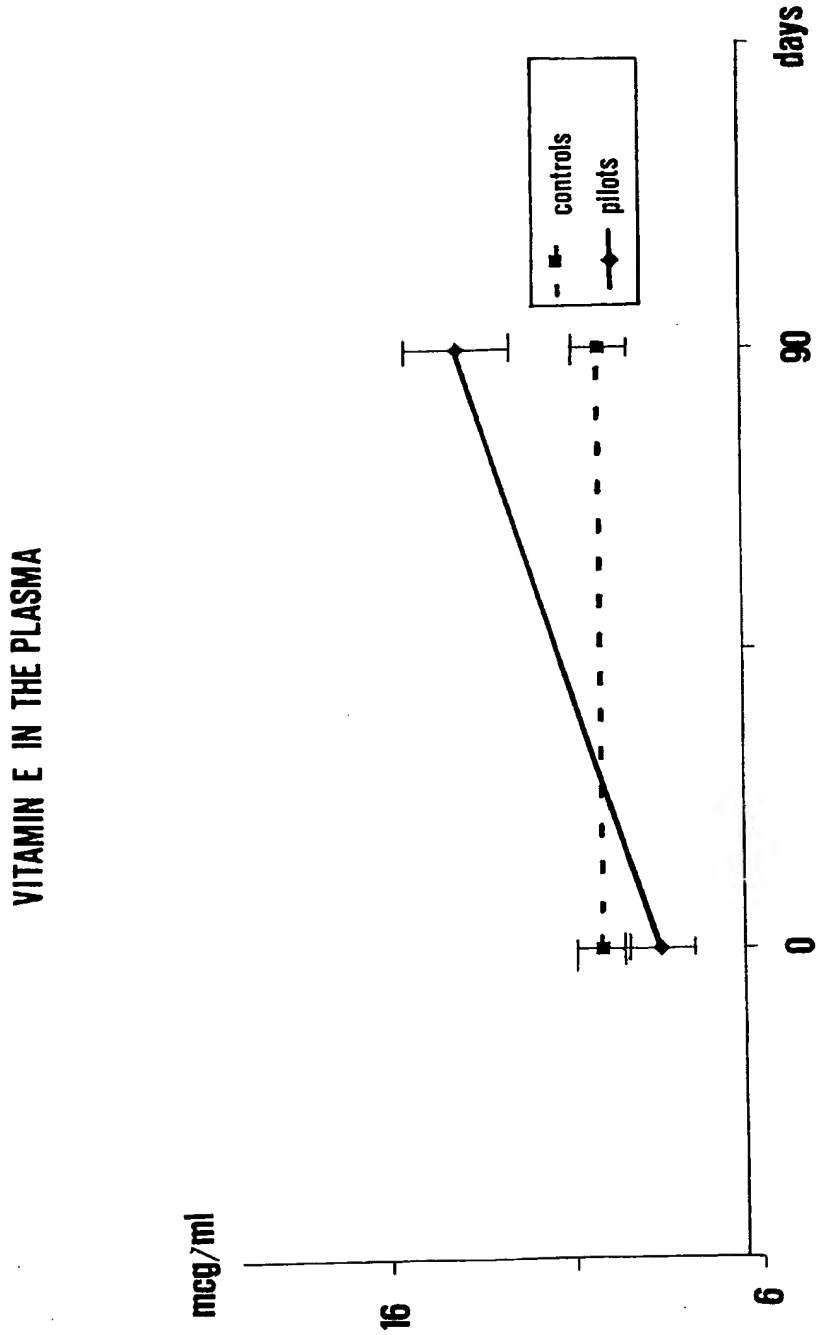

FIG. 10

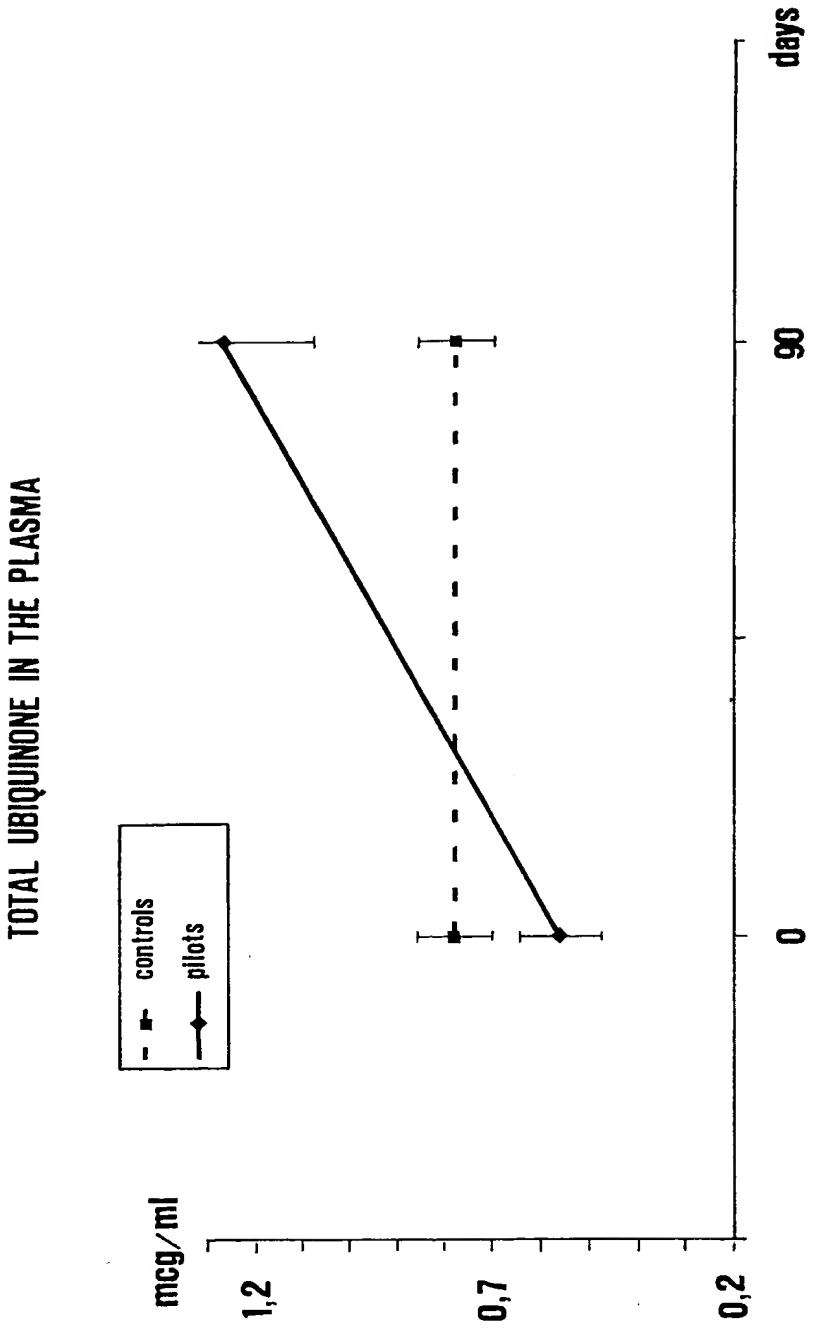
TOTAL UBIQUINONE IN THE PLASMA
controls
pilots
mcg/ml
1,2
0,7
0,2
0
90
days

FIG.11

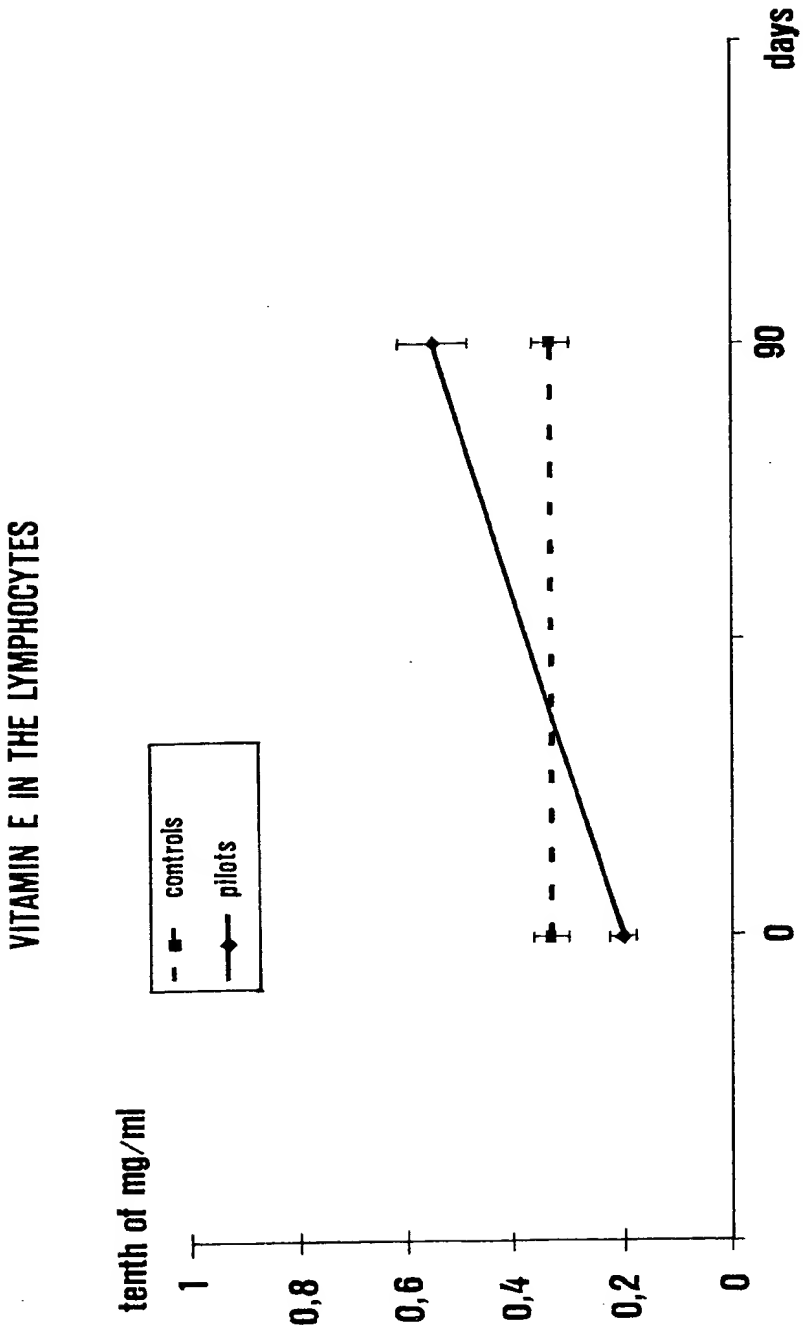
VITAMIN E IN THE LYMPHOCYTES
controls
pilots
tenth of mg/ml
1
0,8
0,6
0,4
0,2
0
0
90
days

FIG.12

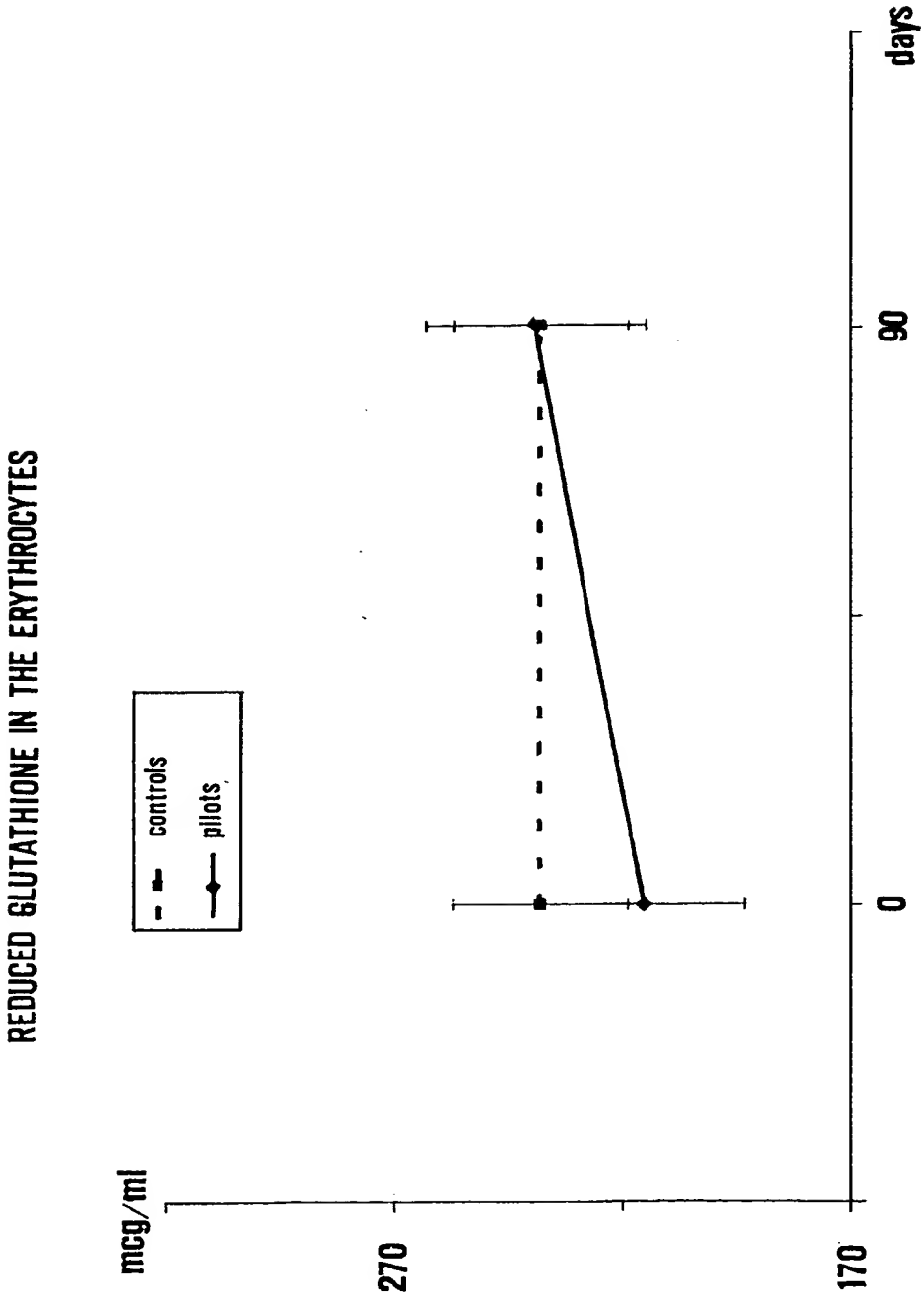
REDUCED GLUTATHIONE IN THE ERYTHROCYTES
controls
pilots
mcg/ml
270
170
0
90
days

FIG.13

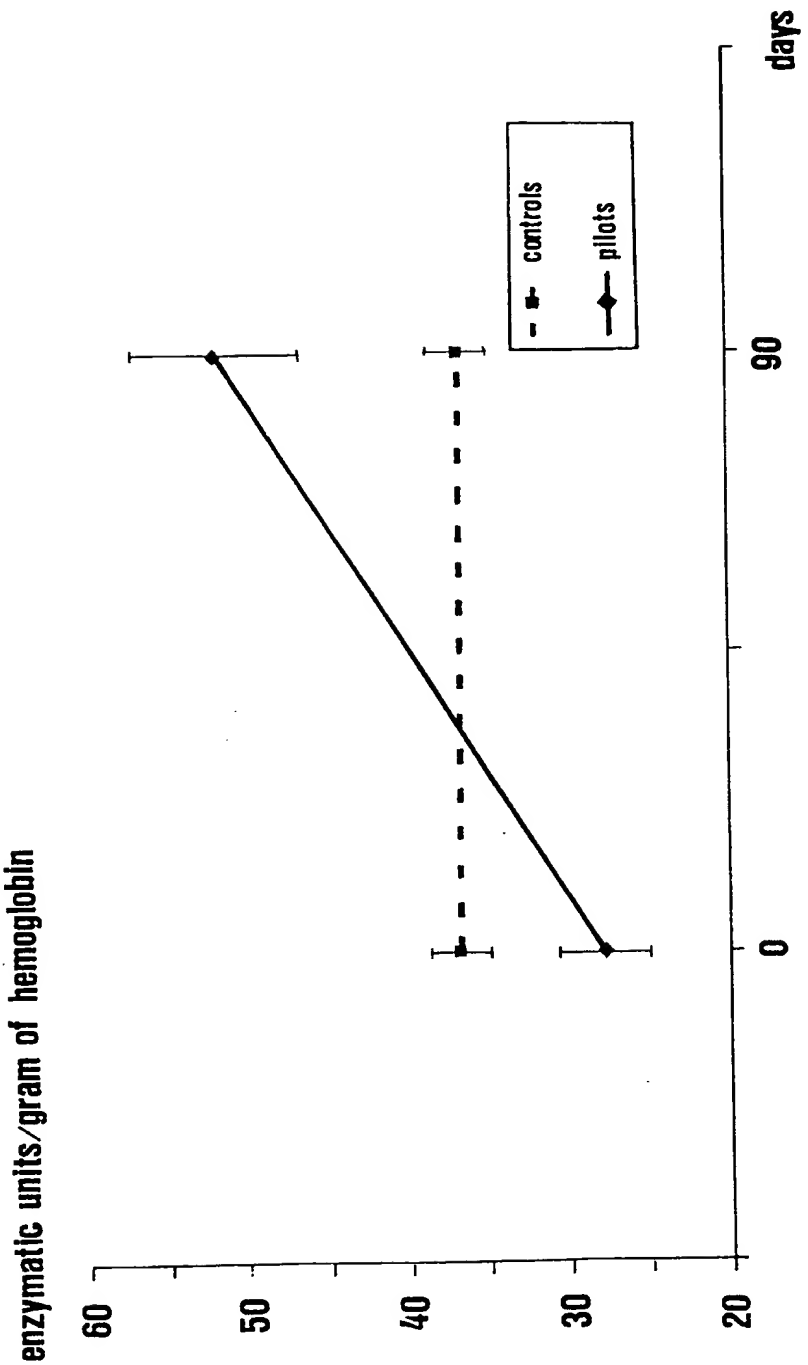
GLUTATHIONEPEROXIDASE IN THE ERYTHROCYTES
enzymatic units/gram of hemoglobin
60
50
40
30
20
0
90
days
controls
pilots

FIG.14

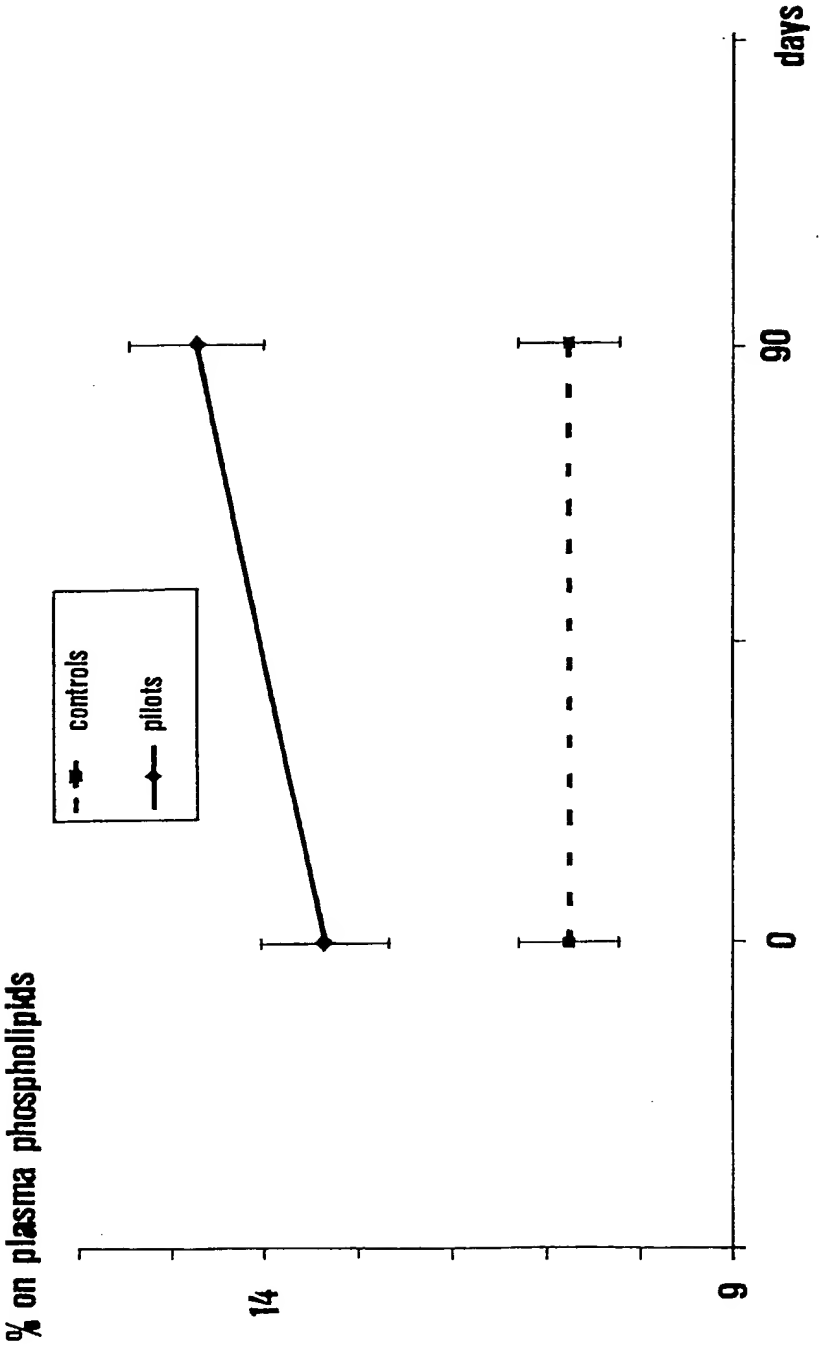
ARACHIDONIC ACID IN THE PLASMA
% on plasma phospholipids
14
9
0
90
days
controls
pilots

FIG.15

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/IT 98/00015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/095 A61K31/355 A61K31/195 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 519 876 A (ISTITUTI FISIOTERAPICI OSPITAL) 23 December 1992 see page 3, line 1 - line 16	1-8
Y	WO 96 17626 A (RYAN PHARMACEUTICALS INC ;UNIV WASHINGTON (US); CANADA NAT RES COU) 13 June 1996 see page 26, line 1 - line 4	1-8
Y	G.M.Carter, "Index of AIDS Treatments: Nutrients and Vitamins" 'Online!, 1996, Available from Internet: <URL:http://www.critpath.org/aric/rtrp/nutrient,htm>, 08.04.98 XP002064225 see whole document	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1998	27/05/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bendl, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/IT 98/00015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0519876 A	23-12-1992	IT 1252717 B	26-06-1995
		US 5290809 A	01-03-1994
WO 9617626 A	13-06-1996	AU 4510596 A	26-06-1996
		CA 2207093 A	13-06-1996
		EP 0796108 A	24-09-1997